

REMARKS

Enclosed herewith in full compliance to 37 C.F.R. §§ 1.821-1.825 is a Substitute Sequence Listing to be inserted into the specification as indicated above. The Substitute Sequence Listing in no way introduces new matter in to the specification.

Also submitted herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a disk copy of the Substitute Sequence Listing. The disk copy of the Substitute Sequence Listing, file "2001-11-13, 0933-0149P St 25.txt" is identical to the paper copy, except that it lacks formatting.

Claims 1 and 3-18 are pending in the present application. Claim 1 has been amended to correct a readily apparent typographical error and correct the claim terminology to properly use Greek letter designations for the interferons. The specification has been similarly amended to replace the interferon designation with the corresponding Greek letters. The sequence listing has been amended to more accurately describe the sequences but the sequences themselves have not been changed. These amendments in no way add new matter to the specification.

The Examiner has restricted the subject matter of the claims into the following two groups.

Group I - Claims 1 and 3-11 drawn to a composition comprising an immunosuppressant and a bioactive peptide to inhibit T cell proliferation.

Group II - Claims 12-18, drawn to a method of amplifying the activity of an immunosuppressant with a composition comprising an immunosuppressant and a bioactive peptide to inhibit T cell proliferation.

The Examiner asserts that the invention of Group I has no special technical feature that defines the invention over the disclosure of de Boer et al., U.S. Pat. No. 5,747,034. De Boer is asserted to disclose a method of treating transplantation rejection using a therapeutically effective amount of (a) an antibody or antigen binding fragment thereof (bioactive peptide) and (b) an immunosuppressive agent, selected from cyclosporin A, FK506, rapamycin and corticosteroids, in a pharmaceutically acceptable excipient.

Applicants traverse this restriction and withdrawal thereof is respectfully requested. DeBoer discloses the prevention of functioning of the B7-1 receptor using a whole monoclonal antibody raised against the receptor. DeBoer also discloses the use of the Fab fragment of the anti-receptor monoclonal antibody. The Fab fragment of deBoer was prepared from the whole monoclonal antibody using known methods. The whole antibody of deBoer is about 160,000kDa and the Fab fragment is about 20-30kDa in size. Thus, both of the binding entities of deBoer are large in size.

The general concept of preventing the function of a receptor through the use of an antibody against the receptor is well-known. It is also a well-known scientific fact that the binding domain of antibodies is made of two separate peptide chains that are bound together through disulfide bridges. Thus, both the whole antibody and the Fab fragment of deBoer are made of two distinct peptide chains bound through disulfide bridges. It is further noted that there is no disclosure in deBoer of the sequences of the Fab fragments that bind to the receptor.

The bioactive peptides of the present invention, on the other hand, are individual peptide chains defined in claim 1 as corresponding to the high-affinity binding/anti-lymphoproliferative site of interferons α , β , ω , τ , or recombinant proteins carrying one

or more of the sequences of the bioactive peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of the the interferons. The molecular weights of the peptides of present invention are at least 10 times smaller than the complex multimeric proteins of deBoer. One skilled in the art would readily recognize that the binding mechanism of an antibody or Fab fragment is substantially different from the binding mechanism of small peptides, such as those of the present invention.

Thus, while the compositions of deBoer may have similar end biological effects to the compositions of the present invention, the antibody and Fab fragments of deBoer do not fall within the group of bioactive peptides of the present invention clearly defined in the claims. As such, deBoer does not disclose the common special technical feature of the present invention, as defined by the bioactive peptides of the present invention. Withdrawal of the restriction and rejoinder of the claims is therefore respectfully requested.

The Examiner further requires an election of species from the following bioactive peptides.

- a) α -peptoferin
- b) albeferon
- c) albebetin; or

d) mixtures thereof.

Claims 11 and 17 have been amended to delete "albebetin" from the list of possible bioactive peptides. One of the exemplified bioactive peptides of the present invention is α -peptoferon, which has an amino acid sequence of LKEKKYSP. As described on page 6, lines 1-7, "albeferon" was made by inserting the 8-mer of α -peptoferon into N-terminus of albebetin, immediately following the initial Met residue. Thus, α -peptoferon is an exemplified bioactive peptide of the invention; albebetin has no bioactivity (recitation of albebetin has been deleted from claims 11 and 17), as disclosed by curve 3 of Figures 3 and 4; and albeferon is an example of a "recombinant protein carrying one or more of the sequences corresponding to...." as recited in claim 1. Albeferon demonstrates that α -peptoferon may be inserted into another protein without loss of activity. Thus, the species as designated by the Examiner are in fact a single species of α -peptoferon. Withdrawal of the election of species, is therefore respectfully requested.

The Examiner further requires an election of species of the following bioactive peptides.

- a) SEQ ID NO:1; or
- b) SEQ ID NO:2.

Applicants note that the peptides of SEQ ID NO:2 are all variants of α -peptiferon that were obtained by screening interferons from different species. See page 8, lines 22-29. Applicants do not believe the species encompassed by SEQ ID NOS:1 and 2 is an unreasonable number for the Examiner to search and exam. As such, withdrawal of the election of species is respectfully requested.

Should the Examiner choose not to withdraw the restriction and election of species, Applicants elect with traverse Group I, claims 1 and 3-11 drawn to a composition, and the species of α -peptiferon and SEQ ID NO:1.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D. (Reg. No. 40,069) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

A marked-up version of the amended portions of the specification and claims showing all changes is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees

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required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17;
particularly, extension of time fees.

Respectfully submitted,

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MARKED-UP VERSION SHOWING AMENDMENTS

IN THE SPECIFICATION

The paragraph beginning at page 4, line 16 has been amended as follows.

Recently, the attention was brought to the long-neglected role of type I interferons (INF- α , β , ω , τ) [(IFN-a,b,w,t)] in the modulation of immune response (Belardelli F. and Gresser I., 1996, Immunol. Today 17, pp. 369-372). The immunomodulating activity of INF- α , β , ω , τ [IFN-a,b,w,t] is very complex and includes:

The paragraph beginning at page 4, line 30 has been amended as follows.

First three immunomodulating properties of type I IFNs (inhibition of lymphocyte proliferation after stimulation with lectins or allogenic cells, prolongation of skin grafts, and inhibition of delayed type of hypersensitivity) are useful for amplification of immunosuppressants' (cyclosporins, FK506 and rapamycin) activity. But other immunomodulating properties of type I IFNs (differentiation towards a Th1 type of immune response; stimulation *in vivo* of long-lived antigen-specific memory CD8⁺ cell cytotoxicity; inhibition of suppressor T cells; enhancement of NK cell cytotoxicity; enhancement of MHC class I antigens expression)

can induce an opposite effect. Indeed, it was observed that a monoclonal antibody directed against the extracellular domain of the human (h)IFN- α [(h)IFN-a] receptor, which inhibits both the binding and biological activity of all the type I IFNs tested, exerted a dose-dependent inhibition of the mixed lymphocyte reaction and induced permanent survival of skin allografts in MHC-divergent Cynomologus monkeys treated with a subeffective dose of cyclosporin A (Tovey, M.G. et al, 1996, J. Leukocyte Biol. 59, pp. 512-517) .

The paragraph beginning at page 5, line 13, has been amended as follows.

In the present invention we suprisingly observed that the physiological effects of immunosuppressants (cyclosporins, FK506 and rapamycin) can be dramatically increased by the simultaneous administration of any one of the immunosuppressants and the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of IFN α [IFN-a] or the recombinant protein having the amino acid sequence corresponding to the said site. Peptides are specially favourable additives since they do not cause harmful symptoms and the acitivity quenching due to the generation of antibodies against larger polypeptides such as natural interferons.

The paragraph beginning at page 5, line 22, has been amended as follows.

Long time ago there was discovered the primary structure homology of hIFN α / β [hIFNs-a/b] and thymus hormone - thymosin α_1 (Tm α_1) [a_1 (TMa $_1$)] (Zav'yalov V. and Denesyuk A., 1984, Doklady Akademii Nauk SSSR 275, pp. 242-246). Comparison of the primary structures of proTm α and hIFN α / β [proTma and hIFNs-a/b] reveals a homology of the prohormone with the IFNs' sites making up the C-terminal helices D and E, however, the highest homology is observed for the C-terminal part of helix D and the N-terminal part of loop DE (Zav'yalov V. et al., 1989, Immun. Lett. 22, pp. 173-182; Zav'yalov V. et al., 1990, Biochim. Biophys. Acta 1041, pp.178-185). One of the synthesized peptides (α -peptoferon) [(a-peptoferon)] overlapping the Tm α_1 -like [TMa $_1$ -like] sequence of hIFN- α_2 [hIFN-a2], effectively competed with hIFN- α_2 , Tm α_1 , proTm α [hIFN-a2, TMa $_1$, proTma] for common receptors on mouse thymocytes (i.e. the K_i of recombinant (r)hIFN- α_2 [(r)hIFN-a2] binding by α -peptoferon [a-peptoferon] is equal to about 10^{-12} M) (Zav'yalov V. et al., 1991, FEBS Lett. 278, pp. 187-189; Zav'yalov V. et al., 1995, Molec. Immun. 32, pp. 425-431). Recently the first example of successful grafting of hIFN- α_2 's Tm α_1 -like [hIFN-a2's TMa $_1$ -like] site to the

design de novo protein albeferon was described (Dolgikh D. et al., 1996, Protein Engin. 9, pp. 195-201). The IFN- α 2 [IFN-a2] fragment corresponded to the TMA₁-like [TMA₁-like] sequence 130-137 was inserted into the N-termini of an albebetin molecule just after the initiatory Met residue. The chimeric protein (albeferon) was expressed in a wheat germ cell-free translation system and tested for its compactness and stability. It has been shown that albeferon is practically as compact as natural proteins of corresponding molecular weight and possesses high stability toward the urea-induced unfolding. To testify the affinity of albeferon to murine thymocyte receptor, the protein inhibitory effect on the binding of radiolabeled [¹²⁵I] α -peptoferon [a-peptoferon] to the receptors has been studied. The albeferon competitive inhibition coefficient (IC₅₀) and the calculated inhibition constant (K_i) are very close to that of rhIFN- α 2 [rhIFN-a2]. It was demonstrated that cell surface binding characteristics correlate with consensus type I IFN enhanced anti-lymphoproliferative activity on the human periferal polymorphonuclear cells (Klein S. et al., 1996, J. Interferon and Cytokine Res. 16, pp. 1-6; Dhib-Jalbut S. et al., 1996, J. Interferon and Cytokine Res. 16, pp. 195-200).

The paragraph beginning at page 6, line 18 has been amended as follows.

The present invention includes the compositions for efficient amplification of immunosuppressive activity of cyclosporins, FK506 or rapamycin by peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] or recombinant proteins having the amino acid sequences corresponding to the said site to decrease therapeutic dose of the both groups of compounds, and as the consequence to avoid their undesirable side effects during organ and tissue transplantation, and treatment of different diseases.

The paragraph beginning at page 7, line 4 has been amended as follows.

These compositions include cyclosporins, FK506 or rapamycin and biologically active peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t], or recombinant proteins having the amino acid sequences corresponding to the said site.

The paragraph beginning at page 7, line 11 has been amended as follows.

FIG. 1 Effect of rhIFN- α 2 [rhIFN-a2] and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN-a2 (a-peptoferon)] on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells.

The paragraph beginning at page 7, line 15 has been amended as follows.

FIG. 2 Effect of rhIFN- α 2 [rhIFN-a2] and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN-a2 (a-peptoferon)] on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4.

The paragraph beginning at page 7, line 19 has been amended as follows.

FIG. 3 Effect of rhIFN- α 2 [rhIFN-a2], albeferon and albebetin on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells.

The paragraph beginning at page 7, line 22 has been amended as follows.

FIG. 4 Effect of rhIFN- α 2 [rhIFN-a2], albeferon and albebetin on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4.

The paragraph beginning at page 7, line 25 has been amended as follows.

FIG. 5 Effect of rhIFN- α 2 [rhIFN-a2] and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN-a2 (α -peptoferon)] on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells in the presence of 20 mM cyclosporin A in cultural medium.

The paragraph beginning at page 8, line 111 has been amended as follows.

In this invention, there was surprisingly observed that certain favourable physiological effects of cyclosporins, FK506 and rapamycin on human cells can be amplified by biologically active peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] or recombinant proteins having the amino acid sequences corresponding to the said site. The peptides and recombinant proteins mentioned above can be readily produced by widely available synthetic or

recombinant techniques. The present invention provides definite improvement of compositions for drugs based on cyclosporins, FK506 or rapamycin aimed for human and higher animals. These compositions include the immunomodulators and biologically active peptides corresponding to the high-affinity binding/anti-proliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t], or recombinant proteins having the amino acid sequences corresponding to the said site. Although all the potentially bioactive peptides or the recombinant proteins containing the amino acid sequences of the peptides were not possible to test experimentally here with the immunomodulator drugs (cyclosporins, FK506 and rapamycin) such structures were revealed by extensive comparisons of available amino acid sequences of interferons from different species by computer and molecular modelling techniques taking into account the experimental data on the localisation of the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] and the experimental data on the competition of type I IFNs for the common receptors. The peptides according to this invention have the advantage of not give rise to antibodies like large polypeptides and natural interferons and thus pepetides as such or bound to carrier molecules can be used for long periods.

The paragraph beginning at page 9, line 1 has been amended as follows.

In the previous studies (Zav'yalov V. et al., 1991, FEBS Lett. 278, pp. 187-189; Zav'yalov V. et al., 1995, Molec. Immun. 32, pp. 425-431) it was demonstrated that only octapeptide corresponding to the 130-137 amino acid residues of hIFN- α 2 [hIFN-a2] had the same or higher affinity to the specific receptors in comparison with recombinant hIFN- α 2 [hIFN-a2]. It is well-known that all type I IFNs compete for the common receptors and can induce the common type I IFN activities. Therefore, it is reasonable to assume that in the process of natural selection the changes in the amino acid sequence of the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] were selected not to abolish the biological activities of the site. Consequently, all type I natural and recombinant IFNs as well as peptides corresponding to their high-affinity binding/anti-lymphoproliferative site, and recombinant proteins having the amino acid sequences corresponding to the said site might reproduce the anti-proliferative activity and amplify immunosuppressive activity of cyclosporins.

The paragraph beginning at page 9, line 14 has been amended as follows.

For the testing of synergism of cyclosporin, FK506 or rapamycin and peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] or recombinant proteins having the amino acid sequences corresponding to the said site we employed the classic anti-lymphoproliferative test system with human peripheral polymorphonuclear cells and human T-lymphoblastoid cell line MT-4. The cell culture conditions and the conditions of the humoral cells in blood circulation are closely related. In fact, in cell cultures, which are commonly used for testing of potential drugs, the conditions are strictly maintained similar to the blood circulation as to the temperature, pH, buffer, minerals, CO₂ and O₂ partial pressures and so on. On the other hand, in this special case the target cells of cyclosporins or the other immunosuppressants and the peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] or recombinant proteins having the amino acid sequences corresponding to the said site being used as the drugs exist specifically in the blood circulation in very equal conditions to the cell cultures. Thus, it is highly predictable that the drug compositions of the present invention can be used as medical drugs for purposes previously used for immunosuppressants alone as the active ingredient in the drug formulations.

The paragraph beginning at page 9, line 31 has been amended as follows.

While the main experimental proof of the present invention lies on the use of peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] or recombinant proteins having the amino acid sequences corresponding to the said site with cyclosporins, also FK506 and rapamycin can be applied with related amplification effect as with cyclosporins. Although the present invention describes effects of peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] or recombinant proteins having the amino acid sequences corresponding to the said site on immunosuppressants such as cyclosporins, FK506 and rapamycin, it is evident that the peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of IFNs- α , β , ω , τ [IFNs-a,b,w,t] or recombinant proteins having the amino acid sequences corresponding to the said site will increase equally well the activities of any other immunosuppressant.

The paragraph beginning at page 11, line 10 has been amended as follows.

Fig. 1 displays, respectively, the effect of rhIFN- α 2 [rhIFN-a2] and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN-a2 (α -peptoferon)] on mitogen (PHA)-driven proliferation of human peripheral polymorphonuclear cells. PHA induced strong lymphoproliferative response that was inhibited by rhIFN- α 2 and α -peptoferon [rhIFN-a2 and α -peptoferon] in a dose-dependent fashion. rhIFN- α 2 and α -peptoferon [rhIFN-a2 and α -peptoferon] demonstrated comparable effects. RhIFN- γ [rhIFN-g] had either no effect or a minimal enhancing effect on the lymphoproliferative response. (1) rhIFN- α 2 [rhIFN-a2]; (2) α -peptoferon [α -peptoferon]; (3) control: PHA; (4) control: cultural medium.

The paragraph beginning at page 11, line 20 has been amended as follows.

Fig. 2 shows the effect of rhIFN- α 2 [rhIFN-a2] and of the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN-a2 (α -peptoferon)] on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4. The proliferation of human T-lymphoblastoid cell line MT-4 was inhibited by rhIFN- α 2 and α -

peptoferon [rhIFN-a2 and a-peptoferon] in a dose-dependent fashion. rhIFN- α 2 and α -peptoferon [rhIFN-a2 and a-peptoferon] demonstrated comparable effects. Similar methods as in Example 1 were employed. (1) rhIFN- α 2 [rhIFN-a2]; (2) α -peptoferon [a-peptoferon].

The paragraph beginning at page 11, line 28 has been amended as follows.

Fig. 3 displays the effect of rhIFN- α 2 [rhIFN-a2] and the designed *de novo* chimeric protein albeferon containing the TMA₁-like [TMA₁-like] sequence 130-137 of the hIFN- α 2 [hIFN-a2] inserted into the N-termini of the protein just after the initiatory Met residue (2), and the designed *de novo* protein albebetin without the hIFN- α 2 [hIFN-a2] fragment (3) on PHA-driven proliferation of human peripheral polymorphonuclear cells. PHA induced strong lymphoproliferative response that was inhibited by rhIFN- α 2 [rhIFN-a2] and albeferon in a dose-dependent fashion. rhIFN- α 2 [rhIFN-a2] and albeferon demonstrated comparable effects. Albebetin had no effect on the lymphoproliferative response. The results show that the hIFN- α 2 [hIFN-a2] fragment corresponded to the TMA₁-like [TMA₁-like] sequence 130-137 is responsible for the anti-lymphoproliferative effect of rhIFN- α 2 [rhIFN-a2]. Similar methods

as in Example 1 were employed. (1) rhIFN- α 2 [rhIFN-a2]; (2) albeferon; (3) albebetin; (4) control: cultural medium; (5) control: PHA.

The paragraph beginning at page 12, line 9 has been amended as follows.

Fig. 4 demonstrates the effect of rhIFN- α 2 [rhIFN-a2], albeferon and albebetin on the proliferation of an IFN-sensitive human T-lymphoblastoid cell line MT-4. The proliferation of human T-lymphoblastoid cell line MT-4 was inhibited by rhIFN- α 2 [rhIFN-a2] and albeferon in a dose-dependent fashion. In this experiment albeferon had higher activity than the sample of rhIFN- α 2 [rhIFN-a2] used but comparable with other data on rhIFN- α 2 [rhIFN-a2] (see Figs. 1-2 and the data described in: Dhib-Jalbut S. et al., 1996, J. Interferon and Cytokine Res. 16, pp. 195-200). Albebetin had no effect on the lymphoproliferative response. The results show that the hIFN- α 2 [hIFN-a2] fragment corresponded to the TMA₁-like [TMA₁-like] sequence 130-137 is responsible for the anti-lymphoproliferative effect of rhIFN- α 2 [rhIFN-a2]. (1) rhIFN- α 2 [rhIFN-a2]; (2) albeferon; (3) albebetin.

The paragraph beginning at page 12, line 20 has been amended as follows.

Fig. 5 displays the effect of rhIFN- α 2 [rhIFN-a2] on PHA-driven proliferation of human peripheral polymorphonuclear cells in the presence of 20 mM cyclosporin A (CsA) in cultural medium. PHA induced strong lymphoproliferative response. The selected concentration of CsA had enhancing effect on the lymphoproliferative response. The administration of extremely low amount of rhIFN- α 2 [rhIFN-a2] (10^{-16} M) totally abolished lymphoproliferative response induced by PHA. The comparable effect on mitogen-driven proliferation of peripheral blood human T-lymphocytes in the presence of 20 mM CsA in cultural medium was observed for the octapeptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN-a2 (a-peptoferon)]. The results demonstrate strong synergism of anti-lymphoproliferative action of CsA and rhIFN- α 2 [rhIFN-a2] or the peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN-a2 (a-peptoferon)]. Related results were obtained with 1-50 mM concentration of FK506 or rapamycin instead of cyclosporin A. Similar methods as in Example 1 were employed. (1) rhIFN- α 2 [rhIFN-a2] and 20 mM CsA; (2) α -peptoferon [a-peptoferon] and 20 mM CsA;

(3) control: cultural medium; (4) control: 20 mM CsA; (5) control: PHA; (6) control: 20 mM CsA and PHA.

The paragraph beginning at page 13, line 5 has been amended as follows.

Fig. 6 displays the effect of albeferon on PHA-driven proliferation of human peripheral polymorphonuclear cells in the presence of 10 mM cyclosporin A (CsA) in cultural medium. PHA induced strong lymphoproliferative response. The selected concentration of CsA had enhancing effect on the lymphoproliferative response. The administration of extremely low amount of albeferon (10^{-12} M) totally abolished lymphoproliferative response induced by PHA. Related results were obtained with 1-50 mM concentration of FK506 or rapamycin instead of cyclosporin A. Fig. 6 also shows that the octapeptide corresponding to the high-affinity binding/anti-lymphoproliferative site of hIFN- α 2 (α -peptoferon) [hIFN- α 2 (α -peptoferon)] which was genetically immobilized on the macromolecular carrier (i.e. on the *de novo* protein albebetin) is biologically active. Similar methods as in Example 1 were employed. (1) albeferon; (2) albeferon and 10 mM CsA; (3) control: cultural medium; (4) control: PHA; (5) control: PHA and 10 mM CsA.

IN THE CLAIMS

Claims 1, 11 and 17 have been amended as follows.

1. (Twice Amended) A composition comprising immunosuppressants, cyclosporins, FK506, or rapamycin and at least one bioactive peptide corresponding to the high-affinity binding/anti-lymphoproliferative site of interferons α , β , ω , τ , [a,b,w,t,] or recombinant proteins carrying one or more of the sequences corresponding to the structures of the bioactive peptides corresponding to the high-affinity binding/anti-lymphoproliferative site of the said interferons for the aim of amplification of immunosuppressants' activities to decrease their therapeutic dose, and as the consequence to avoid their undesirable side effects during organ and tissue transplantation or during treatment of cancers such as lymphomas, leukemias, myelomas, adenocarcinomas, autoimmune and chronic inflammatory diseases, such as rheumatoid arthritis, myasthenia gravis, lupus erythematosus, uveitis, hyperproliferative diseases, such as psoriasis vulgaris, wherein cyclosporins, FK506 or rapamycin can be exploited.

11. (Amended) The composition according to claim 6, wherein the at least one bioactive polypeptide is α -peptoferon [a-peptoferon], albeferon, [albebetin] or a mixture thereof.

17. (Amended) The method according to claim 12, wherein the at least one bioactive polypeptide is α -peptoferon [a-peptoferon], albeferon, [albebetin] or a mixture thereof.